#19
01

P20757.A09

Applicant : Yoshinobu HANYU et al.

Group Art Unit: 1632

Serial No. : 09/810,483

Examiner: Arun Chakrabarti, Ph.D

Filed : March 19, 2001

For : POWDER CONTAINING PHYSIOLOGICALLY ACTIVE PEPTIDE

AMENDMENT UNDER 37 C.F.R. § 1.111

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Responsive to the Office Action of September 16, 2002, reconsideration and withdrawal of the rejections made therein are respectfully requested, in view of the following remarks. Inasmuch as the three-month shortened statutory period was originally set in the Office Action to expire on December 16, 2002, Applicants submit that this response is timely filed. If for any reason the Commissioner determines that an extension of time is required to maintain the pendency of this application, this should be considered to be an express request for any necessary extension of time and authorization for the Commissioner to charge any necessary extension of time fee to Deposit Account No. 19-0089.

REMARKS

Reconsideration and withdrawal of the rejections in the outstanding Office Action is respectfully requested in view of the following remarks.

Preliminary Matters and Interview Summary

Initially, Applicants thank the Examiner for granting an interview, conducted by telephone, on November 27, 2002. Applicants note that the Interview Summary (Form PTO-413) indicates that a separate record of the substance of the interview is not necessary, however; for the record, Applicants express agreement with the Summary. During the interview, Applicants presented arguments as to why the documents of record are insufficient to establish a *prima facie* case of obviousness, and the Examiner disagreed therewith.

Applicants also wish to thank the Examiner for withdrawing the previous § 103(a) rejection.

Reconsideration and withdrawal of the rejections of record are respectfully requested.

Summary of Status of Amendments and Office Action

Claims 33-54 are pending in the application with claims 33-36 being independent.

Claims 34-35 are rejected under 35 U.S.C. § 103(a) over Bergstrand et al. (U.S. Patent 6,103,697).

Claims 33, 36-45 and 49-54 are rejected under 35 U.S.C. § 103(a)over Bergstrand et al. (U.S. Patent 6,103,697) in view of Oyama et al. (U.S. Patent 6,117,434).

Claims 46-48 are rejected under 35 U.S.C. § 103(a)over Bergstrand et al. (U.S. Patent 6,103,697) in view of Oyama et al. (U.S. Patent 6,117,434) further in view of Hughes et al. (U.S. Patent 6,335,316 B1).

Response to § 103(a) Rejection

Claims 34-35 are rejected under 35 U.S.C. § 103(a) over Bergstrand et al. (U.S. Patent 6,103,697). The Office Action asserts that Bergstrand teaches a powder containing a physiologically active peptide, wherein the powder is made up of particles comprising a physiologically active peptide and mannitol, the particles further comprising nonionic surfactant lecithin and a nonionic, organic and a binder polyvinylpyrrolidone. The Office Action acknowledges that Bergstrand does not teach a powder comprising a physiologically active peptide and mannitol in a weight proportion of from 1:1 to 1:50, the non-ionic surfactant in an amount from 0.05 to 3 parts by weight and the water soluble binder in an amount of from 0.05 to 6 parts by weight. However, the Office Action states that it is *prima facie* obvious that the selection of the specific ratios of weights of surfactants and binders represents routine optimization, and therefore, asserts that the claimed invention is obvious.

In response, Applicants once again emphasize that the particular claimed parameter must be recognized as a result-effective variable before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antoine, 559 F.2d 618, 620, 195 U.S.P.O. 6 (C.C.P.A. 1977). A result-effective variable is a variable whose modification achieves a recognized result. Id. at 620. The claims must be based upon optimum or workable conditions. Id.

Applicants are unsure if the Examiner is trying to state that the weight ratio of physiologically active peptide and mannitol is a results-effective variable, or if the weight ratio of the non-ionic surfactant is a results-effective variable, or if the weight ratio of water soluble

binder is a results-effective variable. The rejection only states that the selection of the specific ratios of weights of surfactants and/or binders represents routine optimization and is *prima facie* obvious (apparently, the Examiner means that they are result-effective). But, the Office Action does not the discuss the much more important discovery of the specific weight ratio of the peptide to mannitol, and fails to discuss how this ratio is result-effective. The Office Action also fails to supply any evidence to support the assertion that these values are art-recognized as results-effective, and instead relies solely on the Examiner's belief. Finally, none of Applicants' claims are directed to lecithin as disclosed by Bergstrand, but instead, for those claims that recite lecithin, are directed to hydrogenated lecithin. The Office Action acknowledges this fact on page 6, lines 1-2, when discussing the rejection of claims 33, 36-45 and 49-54. Further, the specification notes at page 19, and discloses in Figure 3, that the use of hydrogenated lecithin results in stabilization of the peptide.

Therefore, contrary to the assertions of the Office Action, Bergstrand is insufficient to establish a *prima facie* case of obviousness for claims 34-35 because the reference cited in the Office Action fails to disclose all of the aspects of Applicants claimed inventions, and the Office Action has failed to show that they are the result of routine optimization.

Applicants respectfully assert that the Office Action misapprehends Applicants' invention and the teachings of Bergstrand. Applicants' claimed invention, as defined in the independent claims is:

> 33. A powder containing a physiologically active peptide, wherein the powder comprises particles which particles comprise a physiologically active peptide

and mannitol in a weight proportion of from 1:1 to 1:50, the particles further comprising per one part by weight of the physiologically active peptide at least one of a nonionic surfactant in an amount of 0.05-3 parts by weight, hydrogenated lecithin, and a binder selected from the group of polyvinylpyrrolidone, polyvinylalcohol, a water-soluble, nonionic, cellulose derivative, and mixtures thereof, in an amount of 0.05-6 parts by weight.

35. A powder containing a physiologically active peptide, wherein the powder comprises particles which particles comprise a physiologically active peptide and mannitol in a weight proportion of from 1:1 to 1:50, the particles further comprising per one part by weight of the physiologically active peptide a nonionic, organic, water-soluble binder in an amount of from 0.05 to 6 parts by weight.

36. A powder containing a physiologically active peptide, wherein the powder comprises particles which particles comprise a physiologically active peptide and mannitol in a weight proportion of from 1:1 to 1:50, the particles further comprising hydrogenated lecithin.

Contrary to the assertions of the Office Action, Bergstrand teaches novel immunomodulators not pharmaceutical preparations of peptides. Bergstrand merely states that pharmaceutical preparations including the disclosed peptides may be made using any of the laundry list of possible excipients disclosed in the cited columns. Moreover, Bergstrand does not discuss the suitable amounts and/or weight ratios of the peptides and excipients for any such

pharmaceutical preparation, and therefore teaches nothing related to Applicants invention. In fact, Bergstrand does not teach anything which would lead to Applicants' claimed invention.

Further, Bergstrands' surfactant teachings appear to be placed in the context of liquid formulations or pressurized (propellants) formulations. For example, col. 3, lines 38-43 recite three types of formulations, pressurized metered dose inhalers, dry powder inhalers, and liquid formulations. Lines 44-52 refer to liquefied propellants which can also act as solvents in pressurized metered dose inhalers and examples of propellants. Finally, lines 53-57, cited in the Office Action as teaching the use of lecithin, notes that low concentrations of surfactants may be used to increase the physical stability of the preparation and that solvents such as ethanol may be used to "increase the solubility of the substances in the propellants." Therefore, it is unclear how one would utilize the teachings of Bergstrand propellants to develop Applicants' invention powder.

Further proof that the Office Action misapprehends Bergstrand's teachings is found at col. 13, lines 58-67 which states

> The active substance may also be delivered through a portable inhaler device suitable for dry powder inhalation. The active substance may be used alone or be combined with a suitable carrier substance such as lactose, mannitol or glucose. Other additives may also be included in the powder formulation by various reasons, such as to increase the stability.

This does not rise to the level concerning powders containing peptides asserted. There is no discussion of the use of lecithin (much less hydrogenated lecithin) in the powder, nor does Bergstrand teach the use of pyrrolidone with the powder. Thus, it is not seen how Bergstrand can

possibly form the basis for a *prima facie* case of obviousness, specifically where the extent of Bergstrands teachings are a powder containing a peptide, and lactose, mannitol or glucose. Here, Applicants' claims recite combination of components at certain weight ratios. As the Office Action has failed to show that the combination of components is obvious or known, *a fortiori,* the specific weight ratios of a non-obvious composition cannot render the composition obvious. Therefore, Applicants respectfully submit that the rejection is untenable and should be withdrawn.

Claims 33, 36-45 and 49-54 are rejected under 35 U.S.C. § 103(a)over Bergstrand et al. (U.S. Patent 6,103,697) in view of Oyama et al. (U.S. Patent 6,117,434). In addition to the above, the Office Action asserts that Bergstrand teach a powder containing a physiologically active peptide for which drying of the aqueous liquid was performed by lyophilization, the peptide is human growth hormone, the average size of the particles is 1-10 μm, and teaches an inhalant composition. The Office Action acknowledges that Bergstrand does not teach hydrogenated lecithin, but asserts that Oyama teaches hydrogenated lecithin as one ingredient of its composition at col. 2, line 32 to col. 3, line 3.

However, contrary to the Office Action's assertions, Bergstrand does not teach a powder having a peptide which was dried from an aqueous liquid by lyophilization at Example 34, because Example 34 does not discuss powders, but, in fact, merely exemplifies the preparation of a purified, isolated peptide, not a peptide in the form of a powder. Therefore, Bergstrand does not teach preparation of a powder by lyophilization as claimed by Applicants.

Further, Bergstrand does not teach human growth hormone at col. 2, lines 15-20 as cited by the Office Action. In fact, col. 2, lines 15-20 states

> We have prepared peptides with cysteine-containing motifs, selected from virus structural proteins e.g. retroviral transmembraneous protein p15E, and human proteins involved in regulation of inflammation, e.g. TGF-β. Peptides were then modified to get optimal immuno-regulatory properties.

It is uncontroverted that human growth hormone does not fall within any of these categories. Therefore, Bergstrand does not teach human growth hormone as claimed by Applicants.

Oyama teaches moisturizing compositions, such as viscous form, gel-like form, oil-in-water type emulsion form and solubilized form, and does not teach a powder. Applicants would also like to remind the Examiner that a similar rejection combining teachings of a powder and teachings of a creme was overcome, specifically the rejection of Maa et al. in view of Knight et al. Powders and cremes are non-analogous arts, involving completely separate technologies, and directed to entirely different issues. The Office Action fails to appreciate this fact, and also fails to set forth a motivation for one creating a powder to look at how a creme solved an allegedly similar problem. Instead, the Office Action asserts that it would be obvious to combine the two cited references from non-analogous arts, simply because the second cited reference teaches a limitation missing in the first.

For the reasons cited above, the combination of Bergstrand and Oyama does not result in Applicants' claimed invention. Therefore, Applicants respectfully submit that the rejection is untenable and should be withdrawn.

Claims 46-48 are rejected under 35 U.S.C. § 103(a)over Bergstrand et al. (U.S. Patent 6,103,697) in view of Oyama et al. (U.S. Patent 6,117,434) further in view of Hughes et al. (U.S. Patent 6,335,316 B1). The Office Action asserts that Hughes teaches human insulin, and therefore, it would have been *prima facie* obvious for one of skill in the art to combine Hughes with Bergstrand and Oyama.

In response, Applicants note that Bergstrand does not teach what the Office Action asserts it teaches, and the combination of Bergstrand, Oyama and Hughes does not give Applicants' claimed invention. Therefore, Applicants respectfully submit that the rejection is untenable and should be withdrawn.

Finally, Applicants respectfully submit that the Office Action uses impermissible hindsight to support the obviousness rejection, in contravention of M.P.E.P. § 2145. A determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor. ATD Corporation v. Lydall, Inc., 48 USPQ2d 1321, 1329 (Fed. Cir. 1998)

In other words, "defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." Monarch Knitting Machinery Corp. v. Sulzer Morat Gmbh, 45 USPQ2d 1977, 1981 (Fed. Cir. 1998) (citing In re Antle, 444 F.2d 1168, 1171-72, 170 USPQ 285, 287-88 (CCPA 1971)).

As Judge Markey explained:

> To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.

W. L. Gore & Associates, Inc. v. Garlock, Inc., 220 USPQ 303, 313 (Fed. Cir. 1983).

Applicants submit that the Office Action "defines the problem in terms of" Applicants' solution, and thus is an impermissible use of hindsight to formulate the rejection. The Office Action has chosen various terms in Bergstrand which allegedly match Applicants claimed invention, but which in reality are either not related to Applicants' invention, teach something entirely different, or do not exist. This is evidence of the use of impermissible hindsight to reach Applicants' claimed invention. Further, the Office Action combines Bergstrand with Oyama and Hughes only because they disclose a limitation missing in Bergstrand.

Further, the Office Action has not set forth any basis for combining the teachings of a powder and the teachings of a creme, nor does it set forth any reason one of ordinary skill in the art would combine Bergstrand and Hughes beyond the fact that Applicants' invention claims insulin. The recitation of the motivation to combine Bergstrand and Hughes is unclear. It is not understood how a teaching that "[s]uch administration can be effective for treating disorders such as diabetes or hyperglycemia" in Hughes and the teaching "[f]or example, delivery by such inhalation devices is advantageously reliable, reproducible, and accurate" from Bergstrand. The Office Action does not point to any teachings in Hughes that "reliable, reproducible, and

accurate" delivery of human insulin is a problem, nor does it point to any teaching in Bergstrand that its powder would work with insulin.

All of this is evidence that the Office Action used impermissible hindsight in fashioning the rejection of claims 33-54.

In view of the above, Applicants respectfully request that this ground of rejection be withdrawn.

Conclusion

For the foregoing reasons, it is believed that all of the claims in this application are in condition for allowance, which action is respectfully requested. Applicants have addressed the Examiner's art based rejection and pointed to the fallacies contained within them, as discussed above. Thus it is believed that all of the claims are in condition for allowance, which action is respectfully requested.

If the Examiner has any questions, or wishes to discuss this matter, the Examiner is respectfully invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,
Yoshinobu HANYU et al.

December 16, 2002
GREENBLUM & BERNSTEIN, P.L.C.
1941 Roland Clarke Place
Reston, VA 20191
(703) 716-1191

Bruce H. Bernstein
Reg. No.29,027

Reg no. 31,296